

Persistent asymptomatic microscopic hematuria in childhood: A single-centered experience

Persistent asymptomatic microscopic hematuria

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Abstract

Aim: This study aimed to evaluate the demographic, clinical, and laboratory findings and prognoses of patients who were followed in a pediatric nephrology department with persistent asymptomatic microscopic hematuria (PAMH) with or without mild proteinuria.

Material and Methods: This retrospective, single-center observational study included 136 patients with PAMH who were referred to our hospital from 2015 to 2020.

Results: The study included 136 children (72 male and 64 female) with PAMH and the mean age at diagnosis was 8.13 ± 3.17 years. The mean follow-up period of the patients was 4.24 ± 2.16 years. The patients were divided into two groups as 107 patients (78.68%) with asymptomatic isolated microscopic hematuria (AIMH) and 29 patients (21.32%) with asymptomatic microscopic hematuria and mild proteinuria (AMHP). No significant difference was determined between the two groups in terms of age, estimated glomerular filtration rate, or family history of renal disease ($p > 0.05$ for each). The male sex ratio was significantly higher among patients in the AMHP group ($p = 0.005$). Glomerular hematuria was detected in 32 patients (23.5%), and 22 of those patients (68.75%) had mild proteinuria accompanying asymptomatic microscopic hematuria at baseline and/or follow-up. The most common histopathological diagnosis was IgA nephropathy. Glomerular pathologies were found to be significantly more common among the AMHP group compared to AIMH ($p = 0.00$). Patients who developed chronic kidney disease (CKD) and hypertension (1.47%) were in the AMHP group.

Discussion: Proteinuria accompanying microscopic hematuria might be a risk factor for the development of CKD. Meticulous long-term follow-up must be performed for isolated microscopic hematuria and renal biopsy should be conducted in selected cases.

Keywords

Isolated Hematuria; Proteinuria; Renal Biopsy; Genetic

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Introduction

Hematuria is one of the most common symptoms among children and is defined as the detection of more than 5 red blood cells in the urine. Hematuria in childhood may be macroscopic or microscopic, and patients may be asymptomatic or symptomatic due to serious renal pathologies [1-4]. Among asymptomatic cases with microscopic hematuria, 50-75% are observed as benign recurrent or persistent hematuria. Persistent asymptomatic microscopic hematuria (PAMH) is a common presenting symptom of renal disorders among children, with a prevalence of 1% to 2%, often being benign and rarely a sign of serious disease. Of this group, as many as one in four will have a normalization of urinalysis in 5 years [3-7]. The most common causes of persistent asymptomatic microscopic hematuria include glomerulopathies (thin basement membrane disease and Alport syndrome), hypercalciuria, and nutcracker syndrome. Most of the time, a detailed medical history, physical examination, and simple laboratory tests facilitate the diagnosis. Kidney biopsy may be required for the early diagnosis of asymptomatic patients with unknown etiology who are at risk of progressive renal disease [1, 3, 8, 9].

In this study, it was aimed to evaluate the demographic, clinical, and laboratory findings and prognosis of patients who were followed in a pediatric nephrology clinic with PAMH.

Material and Methods

In this study, 136 patients aged under 18, who had at least 1 year of follow-up at Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Department of Pediatric Nephrology, between January 2015 and January 2020 and were detected to have microscopic hematuria in 3 consecutive examinations with intervals of 4 weeks or longer were evaluated. The presence of 5 or more erythrocytes in the high magnification field in centrifuged urine examination repeated at least 3 times was considered as hematuria [1]. The presence of a urinary protein creatinine ratio of >0.2 mg/mg or a 24-h protein excretion of >4 mg/m²/h in at least two consecutive evaluations was considered as proteinuria [10]. Patient data were obtained retrospectively from medical records and included clinical and demographic data of the patients, such as age and sex; laboratory findings, such as serum creatinine and albumin; autoimmune screening (anti-nuclear antibody (ANA), anti-double-stranded (ds) DNA antibodies, complement factor 3 (C3) and C4) levels); urinalysis, urinary calcium-to-creatinine ratio or 24-h urinary calcium excretion, and urinary protein-to-creatinine ratio or 24-h urinary protein excretion level; abdominal ultrasonography (USG) findings; renal biopsy findings; and treatment of the disease. Estimated glomerular filtration rate (eGFR) was computed according to the Schwartz formula [11].

Based on the presence of proteinuria, all 136 patients were divided into two groups as 107 patients with asymptomatic isolated microscopic hematuria (AIMH), no proteinuria or macroscopic hematuria, and 29 patients with asymptomatic microscopic hematuria and mild proteinuria (AMHP) (<0.5 g/m²/24 h). Patients who also had severe proteinuria (>0.5 g/m²/24 h), acute or chronic glomerulonephritis, renal insufficiency, a known bleeding diathesis, hypertension, or

chronic systemic illness were excluded from the study. In our clinic, kidney biopsy is performed in patients with PAMH in the presence of a history of microscopic hematuria for at least 2 years, a family history of kidney disease, hypocomplementemia, and/or accompanying proteinuria. No patient received any specific treatment before the renal biopsy. During follow-up, the patients were evaluated in terms of eGFR values, hematuria, proteinuria, and hypertension.

The study protocol was approved by the Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Ethics Committee (Number: E-21/02-102).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables are presented as mean \pm SD and nonparametric variables are presented as median and interquartile range. Categorical variables are presented as numbers and percentages. Student's t-test was conducted to compare parametric variables and the Mann-Whitney U test was conducted to compare nonparametric variables. The chi-square test or Fisher's exact test was used to compare categorical variables. The results were considered statistically significant at $p<0.05$.

Results

The study included 136 children (72 male and 64 female) with PAMH and the mean age was 12.36 ± 3.56 years. The mean age at diagnosis was 8.13 ± 3.17 years and 39% of the patients had a family history. The mean follow-up period of the patients was 4.24 ± 2.16 years. Of the patients, 25% had a family history of kidney stones, 12.5% had a history of hematuria, and 1.5% had a history of chronic kidney disease (CKD). Hypercalciuria was detected solely in one patient and this patient had a family history of stone disease. The mean creatinine level at diagnosis was found to be 0.53 ± 0.1 mg/dL and the mean eGFR level was 114.25 ± 14.02 mL/min/1.73 m². Two patients had reduced serum C3 concentration and ANA and anti-dsDNA were not positive in any patient.

The patients were divided into two groups as 107 patients (78.68%) with AIMH and 29 patients (21.32%) with AMHP. No significant difference was determined between the two groups in terms of age, eGFR values, or family history of renal disease ($p>0.05$ for each). However, the rate of family history of microscopic hematuria unrelated to stone disease was significantly higher in the AMHP group ($p=0.01$). Patients in the AMHP group had a significantly higher male sex ratio ($p=0.005$) and their creatinine values were significantly higher ($p=0.01$). Thirty-two patients underwent kidney biopsy; 22 of these patients were in the AMHP group and 10 patients were in the AIMH group. Glomerular pathology was detected in 28 (21.21%) patients, whereas kidney biopsy was normal in three patients and nonspecific in one patient. The most common histopathological diagnosis was IgA nephropathy (IgAN). Histological findings revealed 10 (31.25%) with IgAN, five (15.62%) with thin basement membrane nephropathy (TBMN), four (12.5%) with mesangial proliferative glomerulonephritis (MsPGN), four (12.5%) with normal biopsies/minor lesions,

Table 1. Clinical and laboratory characteristics of patients with and without mild proteinuria

	AIMH (n=107)	AMHP (n=29)	P
Patient age, years, mean±SD	12.33±3.47	12.5±3.91	0.81
Age at diagnosis, mean±SD	8.01±3.11	8.61±3.38	0.39
Sex (M/F)	46/61	21/8	0.005
Family history of renal disease, n (%)	43 (40.2)	10 (34.5)	0.67
24-h urine proteinuria, mg/m ² /h, mean±SD	1.62±0.93	11.62±3.67	0.00
Serum albumin, g/dL, mean±SD	4.46±2.89	4.28±1.12	0.62
Serum creatinine, mg/dL, mean±SD	0.51±0.09	0.59±0.11	0.01
eGFR, mL/min/1.73 m ² , mean±SD	114.98±14.62	111.54±11.36	0.18
Complete resolution of hematuria, n (%)	52 (48.6)	2 (6.9)	0.00
Hypertension, n (%)	-	2 (6.9)	0.00
Chronic kidney disease, n (%)	-	2 (6.9)	0.00
Follow-up time, years, mean±SD	4.32±2.23	3.92±1.87	0.33

AIMH: Asymptomatic isolated microscopic hematuria; AMHP: asymptomatic microscopic hematuria and mild proteinuria; eGFR: estimated glomerular filtration rate.

three (9.37%) with Alport syndrome, two (6.25%) with focal segmental glomerulosclerosis (FSGS), two (6.25%) with C3 glomerulopathy, one (3.12%) with membranoproliferative glomerulonephritis (MPGN), and one (3.12%) with diffuse proliferative glomerulonephritis. Genetic analyses were performed for nine patients to detect hereditary nephritis; three patients were diagnosed with Alport syndrome by genetics alone and one patient was diagnosed with Alport syndrome by genetics while the kidney biopsy was normal. Hence, glomerular hematuria was detected in 32 patients (23.5%), and in 22 of those patients (68.75%), mild proteinuria was accompanied by asymptomatic microscopic hematuria at baseline and/or follow-up. Glomerular pathologies were found to be significantly more common among the AMHP group compared to AIMH (p=0.00). A comparison of the patients with and without proteinuria is shown in Table 1. No significant difference was determined between the two groups regarding the frequency of histopathological diagnoses (p>0.05). The most common USG finding in patients was stone disease (30.14%), which was present in 41 patients, followed by nutcracker syndrome (10.3%).

Two patients with the histopathological finding of FSGS and COL4A5 mutation who had been diagnosed with Alport syndrome were being followed for stage 2 CKD. In the other patients, no impairment of kidney functions was observed throughout the follow-up period and hypertension was detected in 2 patients. Patients who developed CKD and hypertension were in the AMHP group. None of the patients received any special treatment before the kidney biopsy. Following the renal biopsy, 21 patients with AMHP and six patients with nutcracker syndrome received angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker for proteinuria. None of the patients received immunosuppressive therapy.

Discussion

Hematuria is one of the most common symptoms of urinary system diseases among children and is rarely a sign of a serious disease [12, 13]. It has been revealed in numerous studies that the incidence of glomerular pathology increases and it has a worse prognosis in the presence of proteinuria in patients with

PAMH. Likewise, in our study group, glomerular hematuria was detected in approximately one-fourth of the patients during a mean follow-up period of 4.24±2.16 years. Mild proteinuria accompanied asymptomatic microscopic hematuria at baseline and/or in follow-up in 68.75% of patients in this group.

Persistent asymptomatic microscopic hematuria is mostly detected in children aged between 9 and 9.5 years old and the male/female ratio was reported to range between 0.5 and 1.7 [9, 12]. In our study, the median age at diagnosis was 8.13±3.17 years and the male/female ratio was 1.1. No significant difference was determined between patients with AIMH and patients with AMHP in terms of age (p=0.36); however, the male sex ratio was significantly higher among patients in the AMHP group (p=0.005). Urolithiasis is one of the frequently detected ultrasound findings in pediatric patients presenting with gross or microscopic hematuria with or without coexisting abdominal pain, flank pain, or vomiting [14]. Similarly, in our study, the most common USG finding in patients was stone disease (30.14%).

Since hereditary nephropathies can only present with microscopic hematuria in the early stages of the disease, periodic follow-up of PAMH patients for proteinuria is recommended [15, 16]. Considering the data from seven studies involving 1092 children, it was noted that more than 40% of patients with AIMH and more than 80% of patients with AMHP had underlying pathologies. While a limited assessment is reasonable for a child with AIMH, it was underscored that a comprehensive medical history and laboratory examination may be necessary for a child with AMHP. Meticulous long-term follow-up and the scheduling of renal biopsy in selected cases are recommended for these patients [3, 12, 13]. On the other hand, there is no definite consensus on when kidney biopsy should be performed in children with PAMH [13, 15]. In our study, mild proteinuria was detected in 29 patients (21.32%). In some studies, a family history of kidney disease was determined to be significantly more common among patients with AMHP compared to AIMH [9, 12]. However, in our study, no difference was found between patients with AIMH and AMHP regarding family history of kidney disease (p=0.57), although a family history of microscopic hematuria unrelated to stone disease was significantly more common in the AMHP group (p=0.01). These differences may be due to the varying numbers of patients included in the studies and the number of patients with a family history of kidney disease.

Histopathologically, normal biopsies, minor lesions, IgAN, and non-IgA MsPGN accounted for the majority of patterns in PAMH, followed by TBMN, Alport syndrome, MPGN, and FSGS. However, the histopathological diagnoses were different between the AIMH and AMHP groups. Normal biopsies or minor lesions were the most common findings among the AIMH group, whereas IgAN was the most common finding among the AMHP group, which indicates a positive correlation between the severity of clinical characteristics and the histopathological pattern [9, 12, 16, 17]. In our study, glomerular hematuria was detected in 32 patients (23.5%), while three patients were diagnosed only through genetic examination and one patient was diagnosed via genetic examination though kidney biopsy was normal. The most common histopathological diagnosis was IgAN.

The relationship between microhematuria and negative renal outcomes has been reported in several studies [7, 12, 13]. Lin et al. [18] analyzed 573 school-age children in Taiwan and demonstrated that 46.4% of children had persistent AIMH while 14.3% of children had AMHP; they also suggested that children with AIMH are at the same risk for significant glomerulopathies as children with proteinuria. In addition, several studies suggest that long-term outcomes in AIMH are associated with an unfavorable prognosis and that kidney biopsy should be performed at an early stage, and the urinary albumin/creatinine ratio has been shown to be a good predictor for identifying patients at high risk for glomerulopathies [19, 20]. Lee et al. [21] found a relatively high rate of pathological abnormalities on kidney biopsy in a group with microscopic hematuria combined with AMHP compared to the AIMH group. Consistent with this finding, in our study, glomerular pathology was found to be significantly more common in the AMHP group ($p=0.00$). Two patients with the histopathological finding of FSGS and COL4A5 mutation who had been diagnosed with Alport syndrome were being followed for stage 2 CKD. In the other patients, no impairment of kidney functions was observed throughout the follow-up period and hypertension was detected in 2 patients. Patients who developed CKD and hypertension were in the AMHP group. Thus, our findings are favorable in terms of not performing an early biopsy in the course of AIMH. The main limitations of this study were that it had a retrospective design, reflected the data from a single center, and enrolled a limited number of patients.

Conclusion

Proteinuria may be a significant risk factor for the occurrence of CKD when it is accompanied by microscopic hematuria. As the prognosis of AIMH patients is favorable, a kidney biopsy can be scheduled in the future depending on the follow-up of the patients. However, an early kidney biopsy may be considered when hematuria is accompanied by proteinuria and has a family history.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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